El patrón de activación de los circuitos cerebrales con DBS en la EP y la distonía evaluado por fMRI

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El patrón de activación cerebral en respuesta a DBS

- Hipótesis: La estimulación cerebral profunda óptima produce una signa de activación cerebral medida por fMRI.
- Métodos:
- Asegurar que las sequencias 3T fMRI son seguras en pacientes con DBS
- Ver que son las señales fMRI obtenidas con el paciente programado para el beneficio clínico máximo
- Pacientes con EP con STN DBS

JNS

CLINICAL ARTICLE

3-Tesla MRI in patients with fully implanted deep brain stimulation devices: a preliminary study in 10 patients

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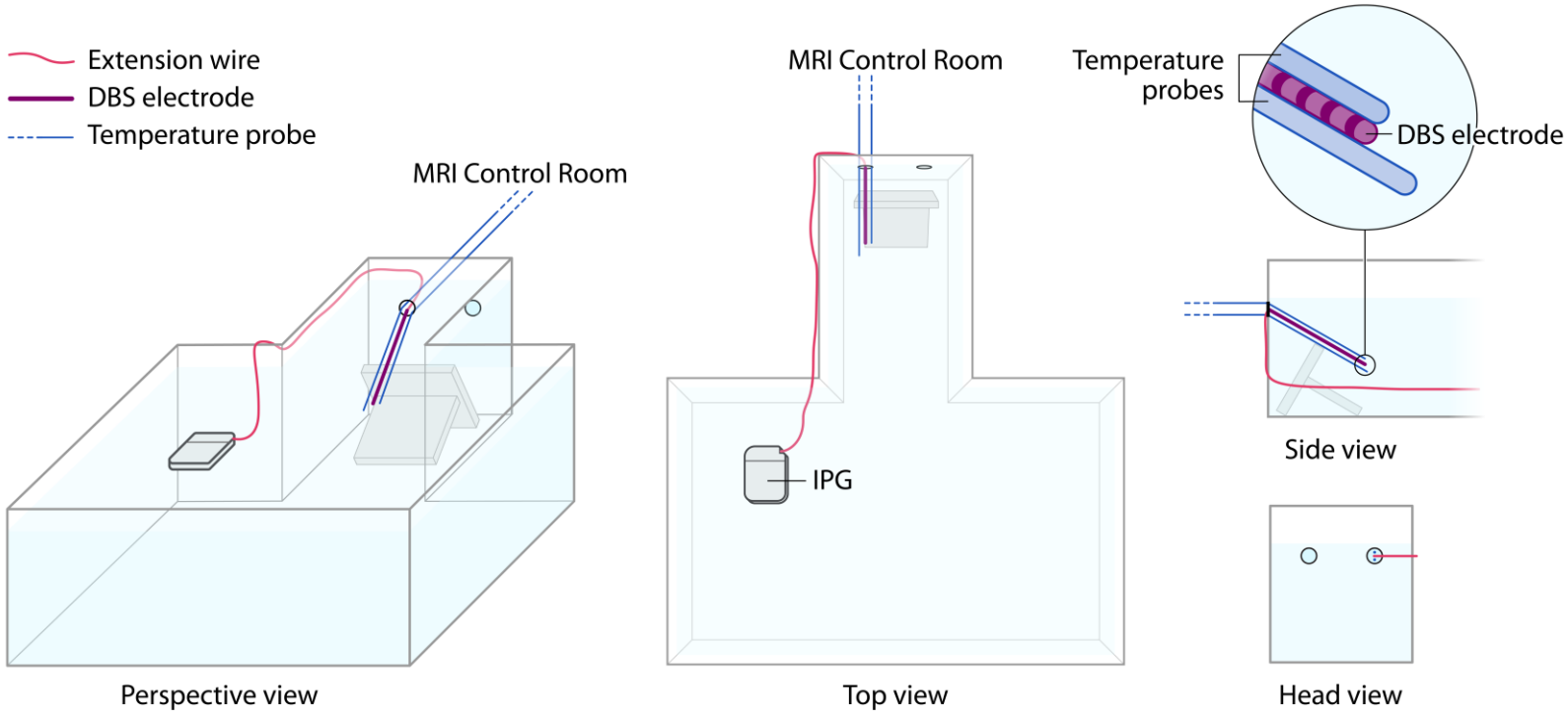
Safe acquisition of 3T MRI in DBS patients

Methods



Functional MRI Safety and Artifacts during Deep Brain Stimulation: Experience in 102 Patients

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Conflicts of interest are listed at the end of this article.

See also the editorial by Martin in this issue.

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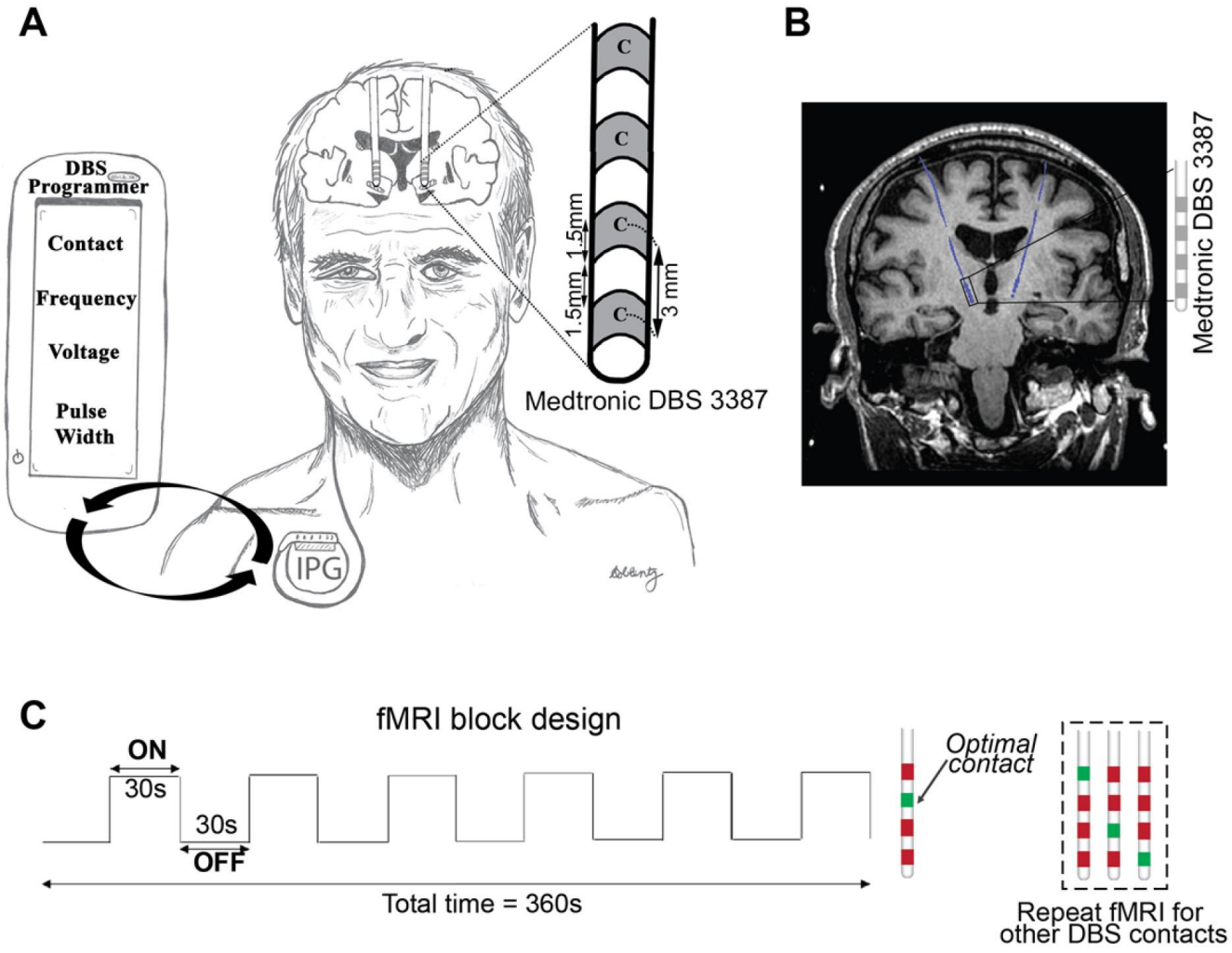
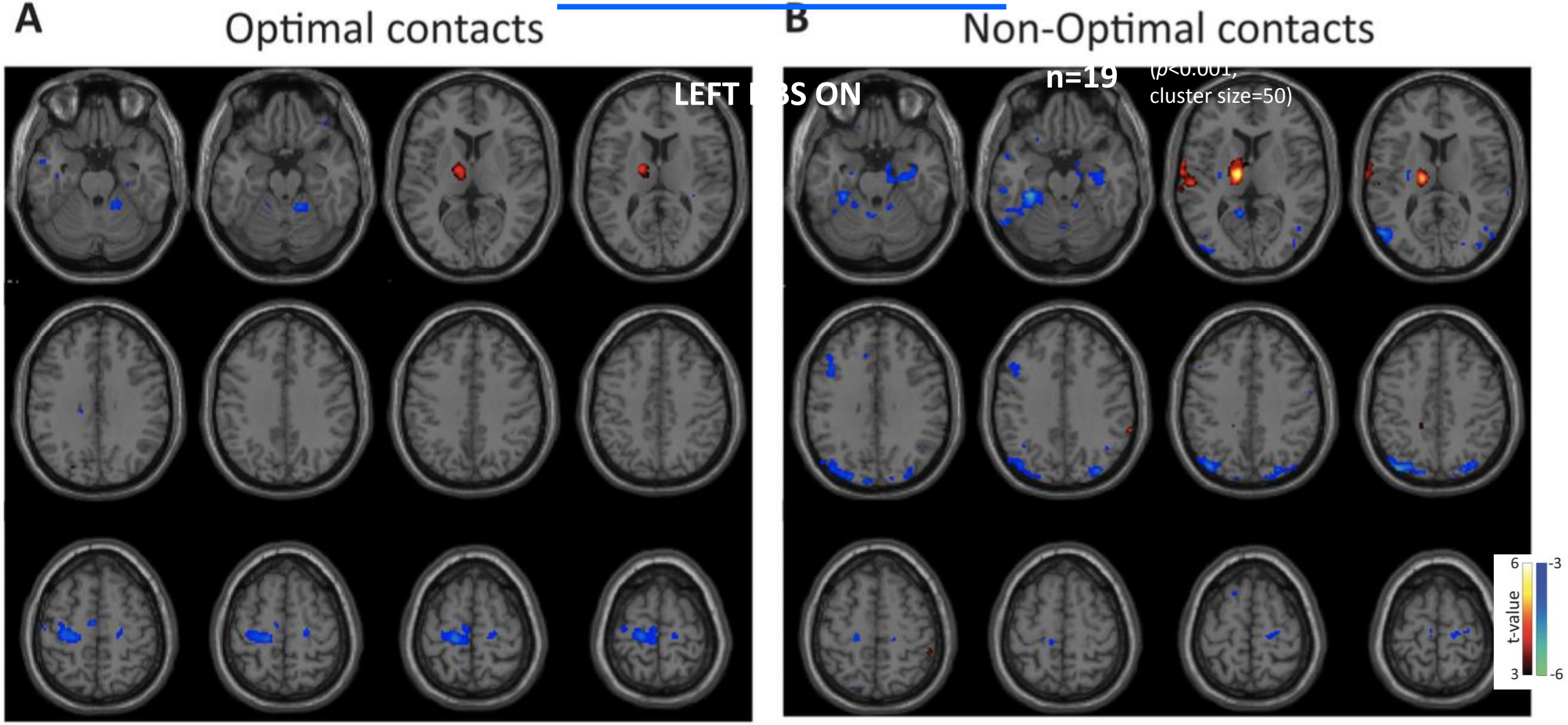
fMRI-with DBS
Methods

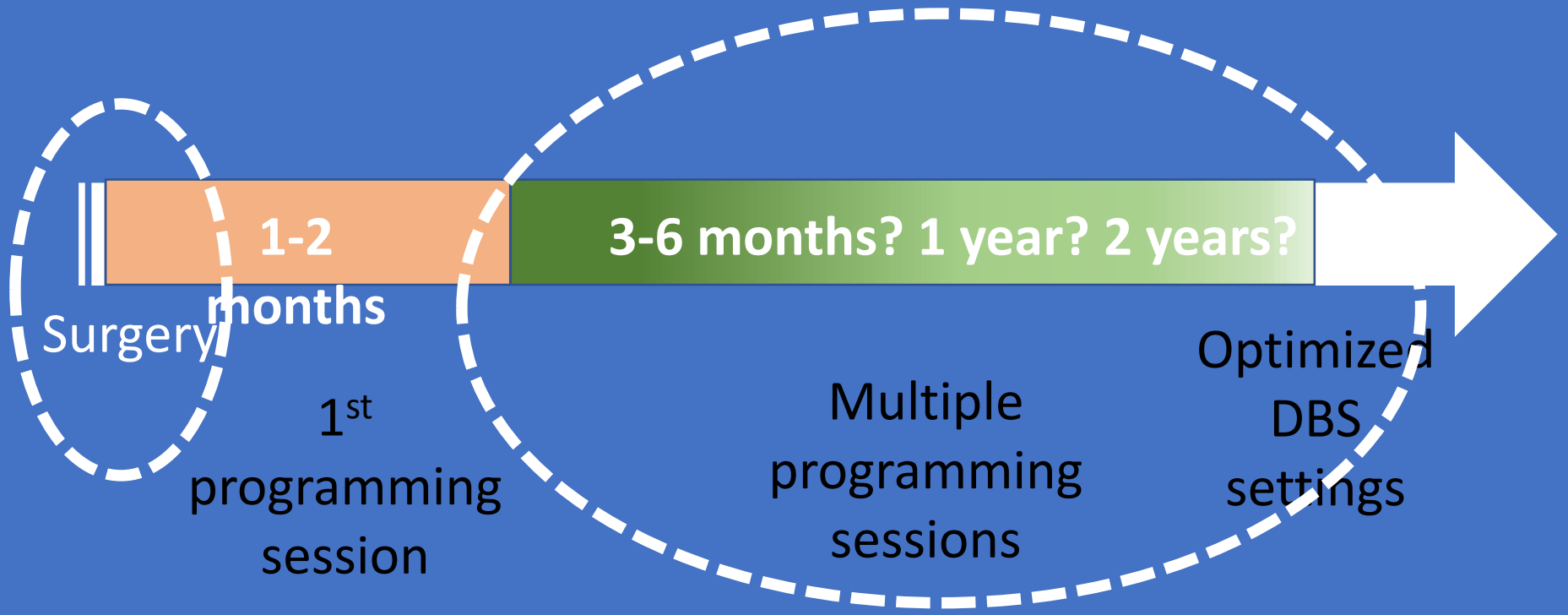


Boutet et al,, Nature Comm

MRI-based DBS programming
Results N=20

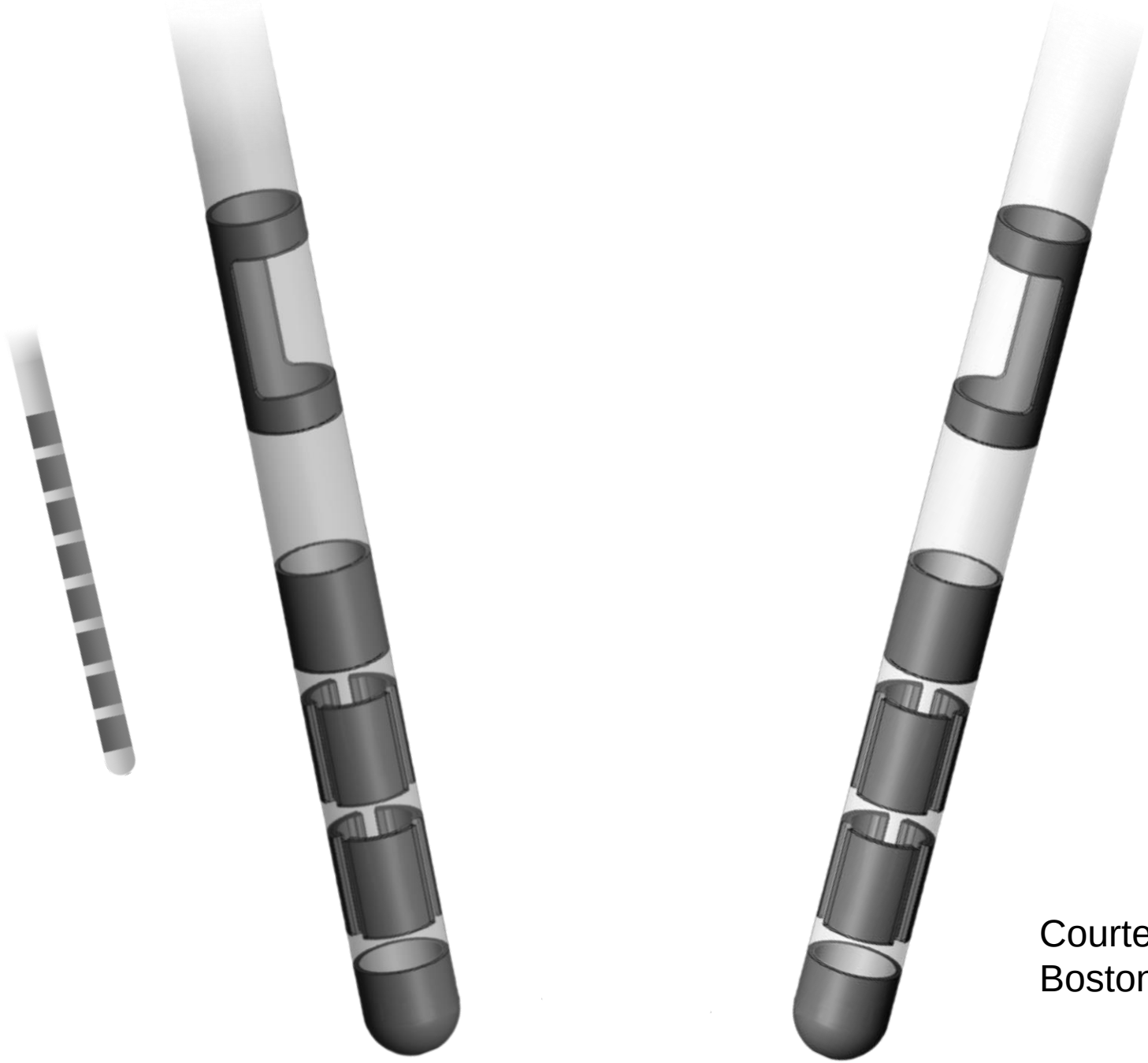


Hipótesis: Dado que conocemos el patrón de actividad cerebral que se correlaciona con un buen resultado clínico, ¿podríamos usar fMRI para guiar la programación de DBS?



PD and DBS

• Hipótesis: Dado que conocemos el patrón de actividad cerebral que se correlaciona con un buen resultado clínico, ¿podríamos usar fMRI para guiar la programación de DBS?



Increasing complexity of DBS electrodes, large number of possible stimulation parameters

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ARTICLE

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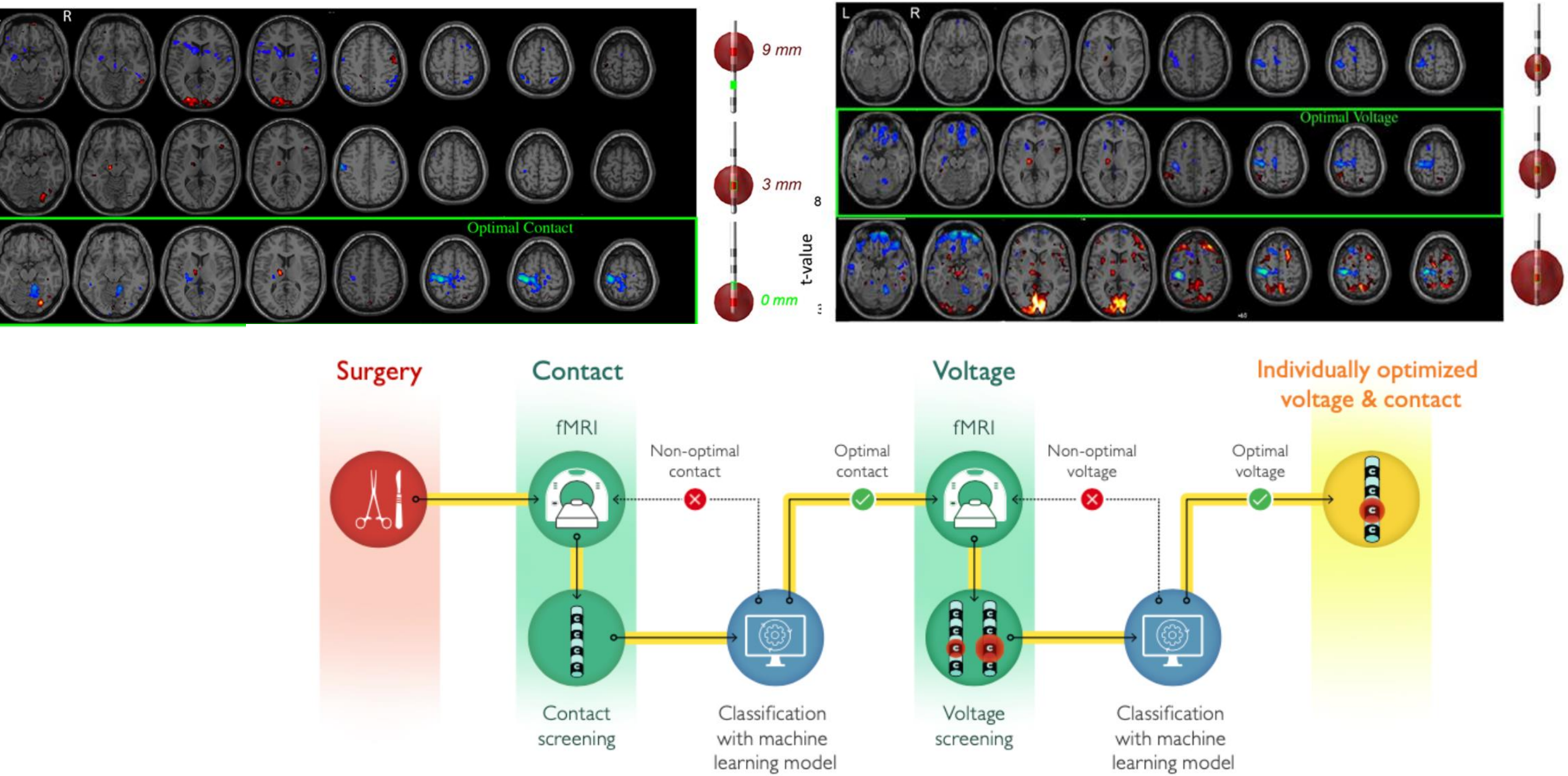
Predicting optimal deep brain stimulation parameters for Parkinson's disease using functional MRI and machine learning

Alexandre Boutet[1,2,8], Radhika Madhavan[3,8], Gavin J. B. Elias[2], Suresh E. Joel[4], Robert Gramer[2], Manish Ranjan[2], Vijayashankar Paramanandam[5], David Xu[2], Jurgen Germann[2], Aaron Loh[2], Suneil K. Kalia[2], Mojgan Hodaie[2], Bryan Li[1], Sreeram Prasad[5], Ailish Coblentz[1], Renato P. Munhoz[5], Jeffrey Ashe[3], Walter Kucharczyk[1], Alfonso Fasano[5,6,7] & Andres M. Lozano[2,6,7]✉

predicción de parámetros óptimos de DBS mediante fMRI

MRI-based DBS programming

- Methods:
  - Pacientes con EP con STN DBS
  - Pacientes de novo aún no programados N=19
  - Ajustamos la estimulacion hasta producir la segnal fMRI deseada
  - Se entrega el paciente con el estimulador “Off” a los neurologos
  - Comparamos los parámetros de la estimulación derivados por el fMRI a los que consigue el neurologo con programacion tradicional



Supplementary Fig. S10: **fMRI-based DBS programming.** Proposed fMRI-based programming

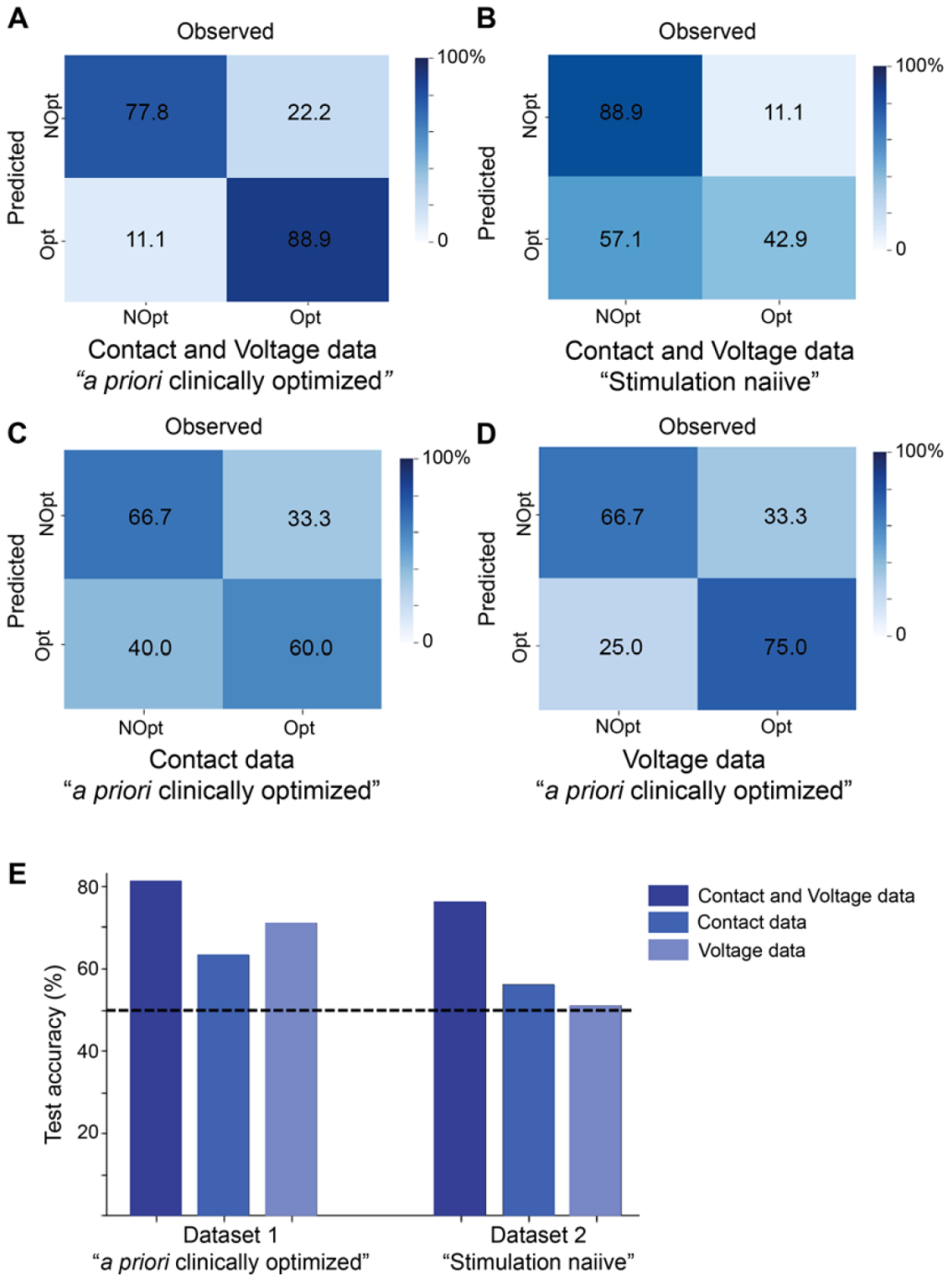
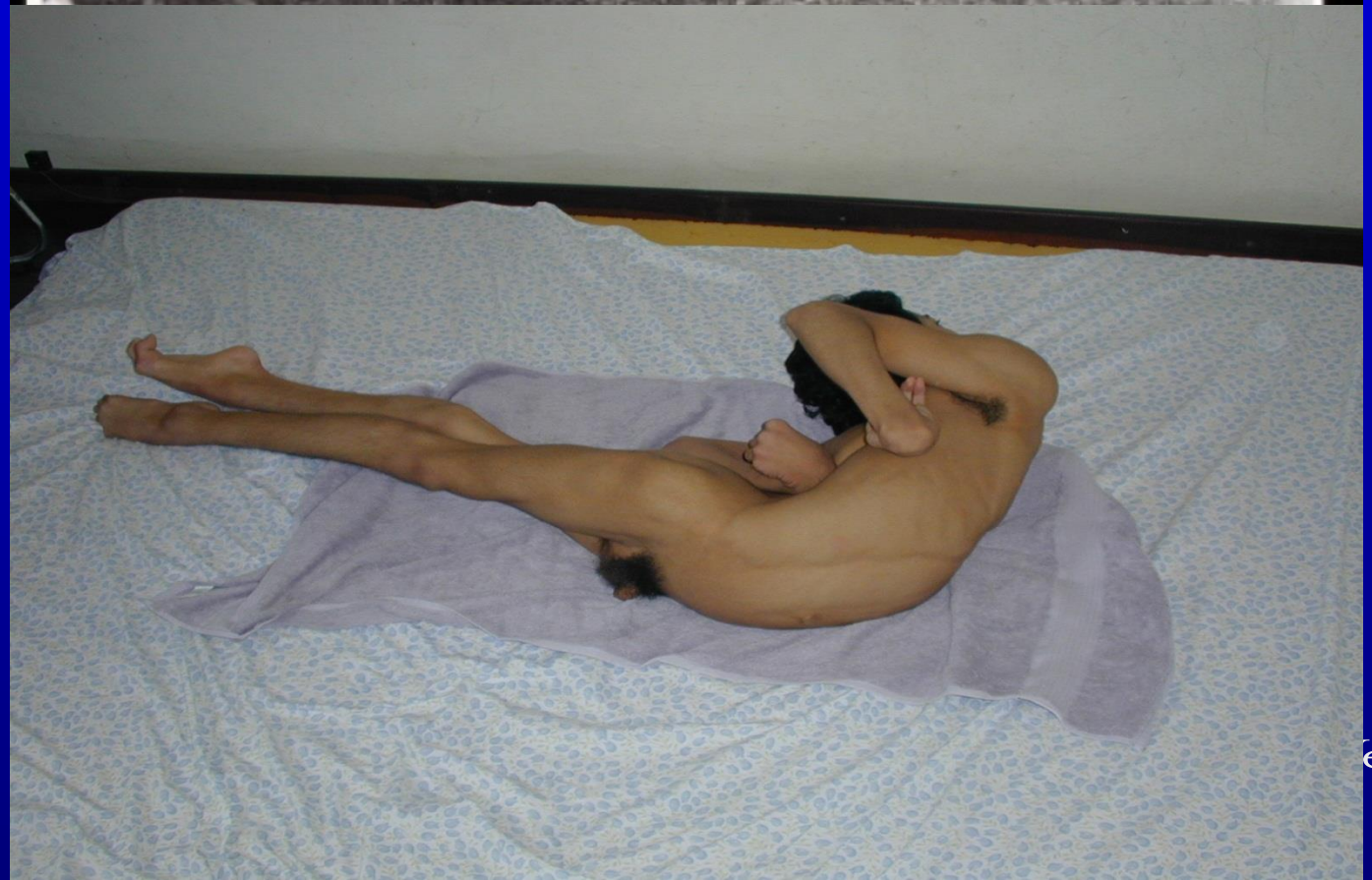


Figure 5: fMRI responses predict optimal DBS parameters. Confusion matrices depicting the performance of classifiers trained to identify optimal DBS settings using features from (A) contact and voltage cohorts, (C) contact cohort alone, and (D) voltage cohort alone in an independent test set ($n = 9$ *a priori* clinically optimized patients). (B) Confusion matrix depicting the performance of the classifier trained to identify optimal DBS settings using features from contact and voltage cohorts in an independent test set (n = 9 stimulation naïve patients). (E) Summary of performance (overall accuracy) for classifiers in A-D. Bars from dataset 2 depict classifier accuracy on stimulation naïve patients. NOpt = Non-optimal; Opt=Optimal.



estern Hospital

Time course of DBS/lesions in Dystonia

- Beneficio retardado y progresivo con la palidotomía y la ECP en dystonia
- Falta si la efectos clínicos inmediatos complica la programación
- Riesgo de abandonar los parámetros de estimulación óptimos porque no se ha permitido suficiente tiempo para producir beneficios clínicos
- El ensayo y error se convierte en ensayo y, sobre todo, en errores
-

Neural correlates of optimal deep brain stimulation for dystonia

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Submitted

Patient #	Sex	Age at scan	Disease subtype	Aetiology	Disease duration at time of scan (years)	Duration of DBS at time of scan (years)	Scale	Best % improvement
1	F	71	cervical dystonia	Idiopathic	22	10	TWSTRS	100%
2	M	67	cervical dystonia	Idiopathic	31	8	TWSTRS	57%
3	F	58	cervical dystonia	Idiopathic	36	8	TWSTRS	100%
4	M	67	generalized dystonia	Idiopathic	61	8	BFMDRS	62%
5	M	68	generalized dystonia	DYT6	54	13	BFMDRS	76%
6	M	76	truncal dystonia	Idiopathic	60	12	BFMDRS	75%
7	M	75	cervical dystonia	Idiopathic	21	8	TWSTRS	42%
8	F	56	cervical dystonia	Idiopathic	31	2	TWSTRS	44%
9	F	51	cervical dystonia	Idiopathic	26	4	TWSTRS	50%
10	F	71	cervical dystonia	Idiopathic	30	2	TWSTRS	60%
11	F	24	generalized dystonia	DYT1	14	2	BFMDRS	100%

Table 2. Participant demographics. BFMDRS = Burke-Fahn Marsden Dystonia Rating Scale; DBS = deep brain stimulation; DYT1 = dystonia 1; DYT6 = dystonia 6; F = female; M = male; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale

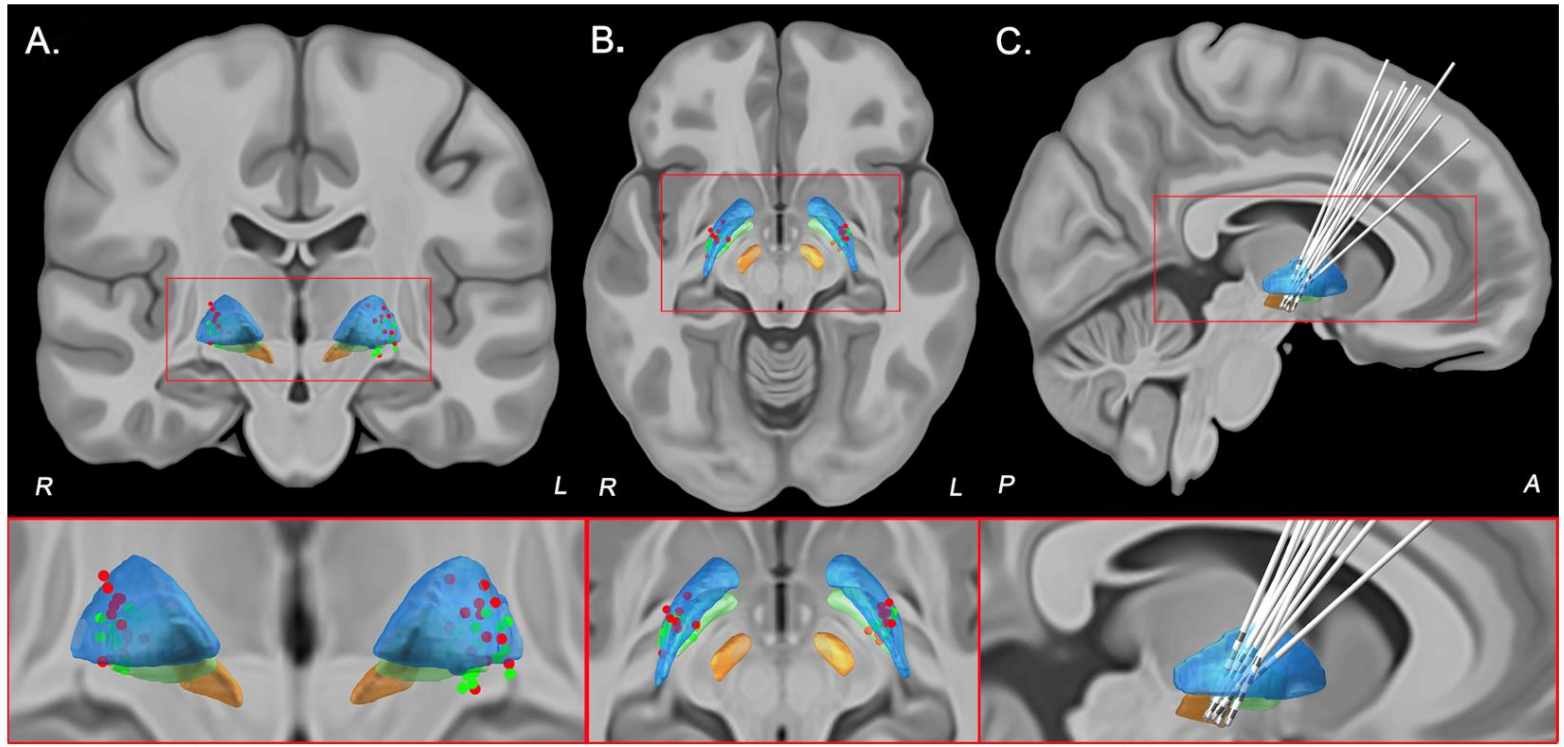


Figure 2. Distribution of active electrode contacts. Point clouds for the active cathodes on optimal (green points) and non-optimal (red points) DBS stimulation settings are shown overlaid on coronal (A) and axial (B) slices of a T1-weighted standard brain template (Neudorfer *et al.*, 2020) in relation to various structures of interest. The electrode trajectories of all 11 patients are shown in C. The bilateral GPe are shaded blue, GPi are light green, and STN are orange. Mean x, y, z coordinates of left and right optimal cathodes [left: -22(±2), -7(±2), -4(±3); right: 21(±1), -7(±2), -2(±2)] and non-optimal cathodes [left: -23(2), -7(±3), -2(±4); right: 22(±1), -7(±2), -1(±3)] were not significantly different (right x: $p = 0.84$, y: $p = 0.37$, z: $p = 0.27$; left x: $p = 0.91$, y: $p = 0.37$, z: $p = 0.13$). DBS = deep brain stimulation; GPe = external globus pallidus; GPi = internal globus pallidus; STN = subthalamic nucleus.

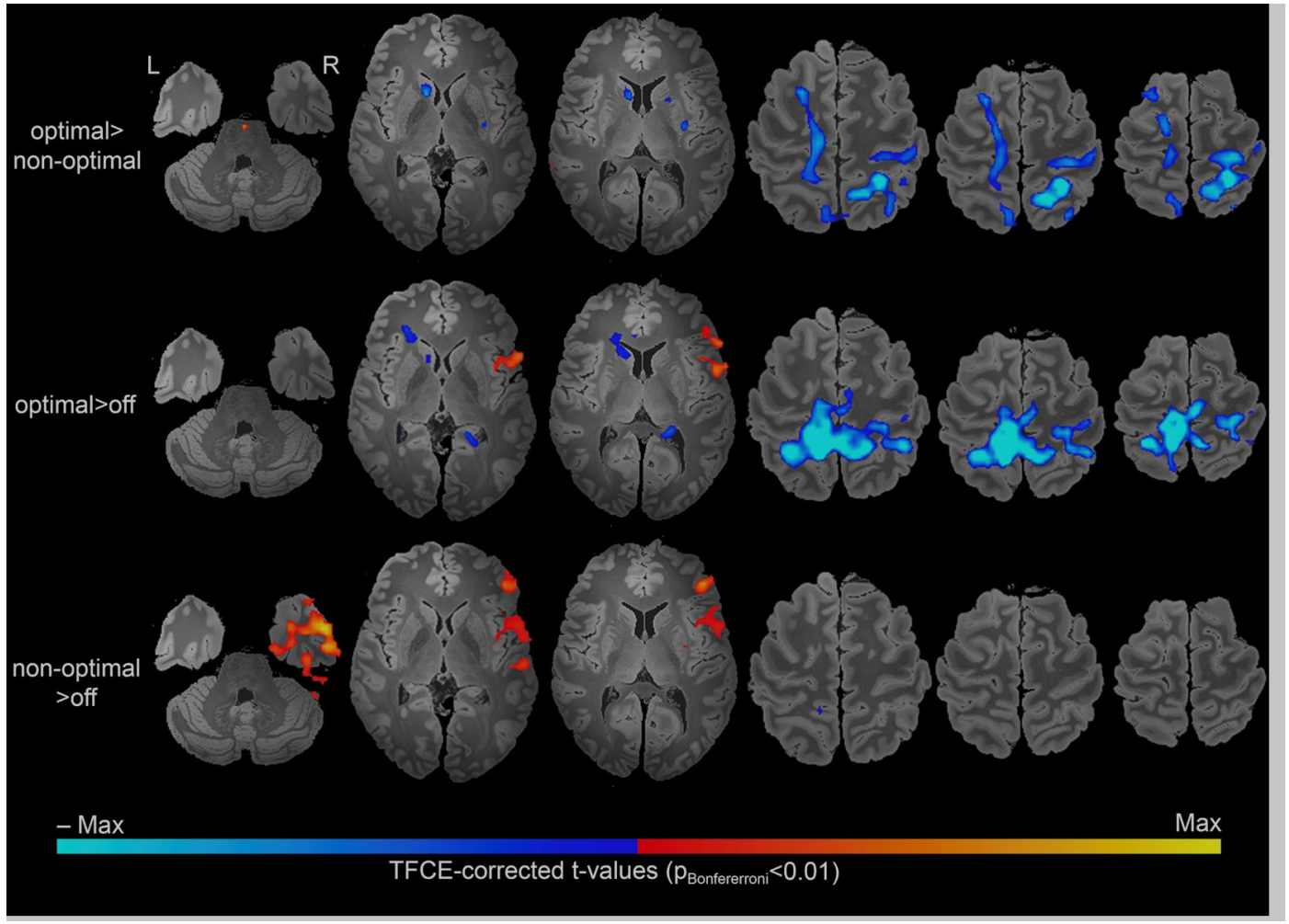


Figure 3. DBS on optimal settings is associated with sensorimotor cortex deactivation. Areas of significant (p_{cor}<0.01, bonferroni corrected) ALFF change with DBS $ON_{non\text{-}optimal}$>DBS OFF (left column) and DBS $ON_{optimal}$>DBS OFF (right column) are shown overlaid on a axial slices of standard brain template (FLASH brain). Areas of significant activation are shown in 'warm' colours and areas of deactivation are shown in 'cool' colours. ALFF = amplitude of low frequency fluctuations; DBS = deep brain stimulation; L = left; R = right; TFCE = threshold free cluster enhancement

Los cambios en la amplitud de las fluctuaciones de baja frecuencia en áreas específicas del cerebro se correlacionan con el resultado clínico en la distonía

Área premotora
Giro post central
Lóbulo parietal superior

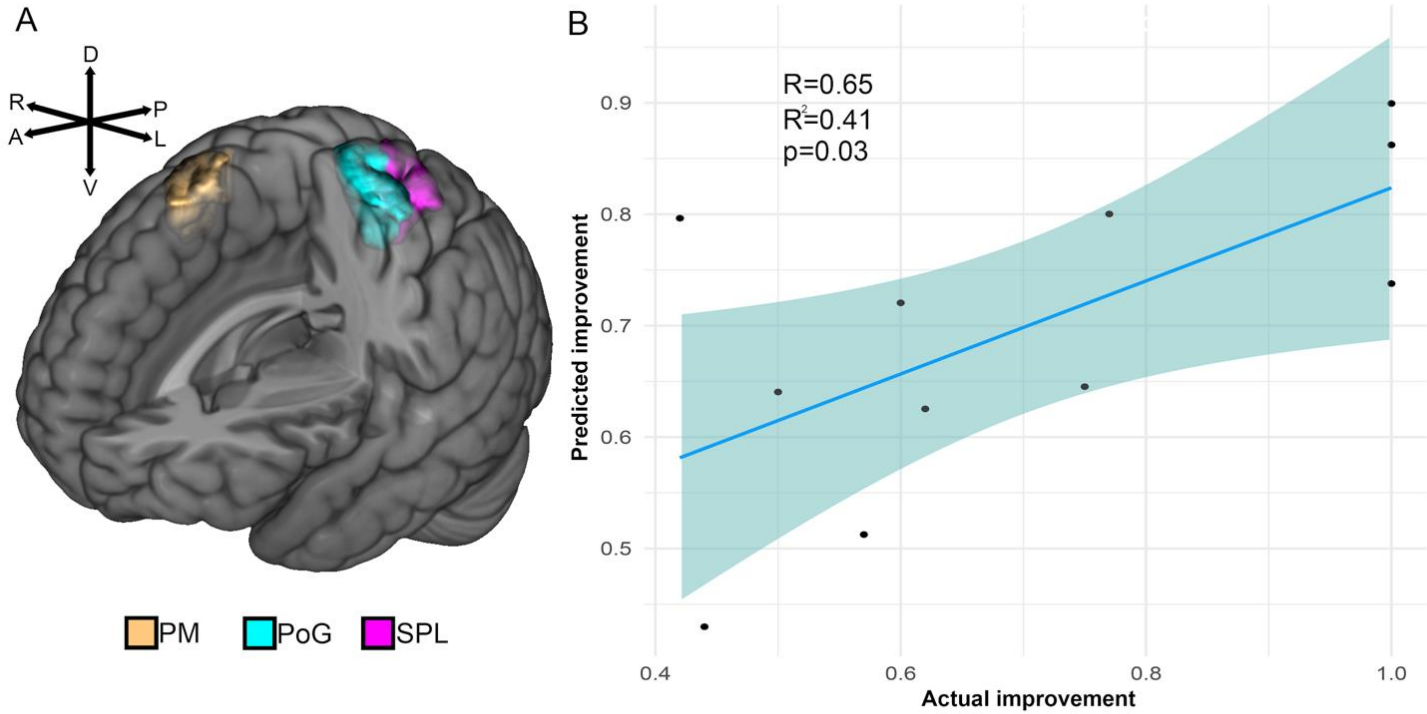
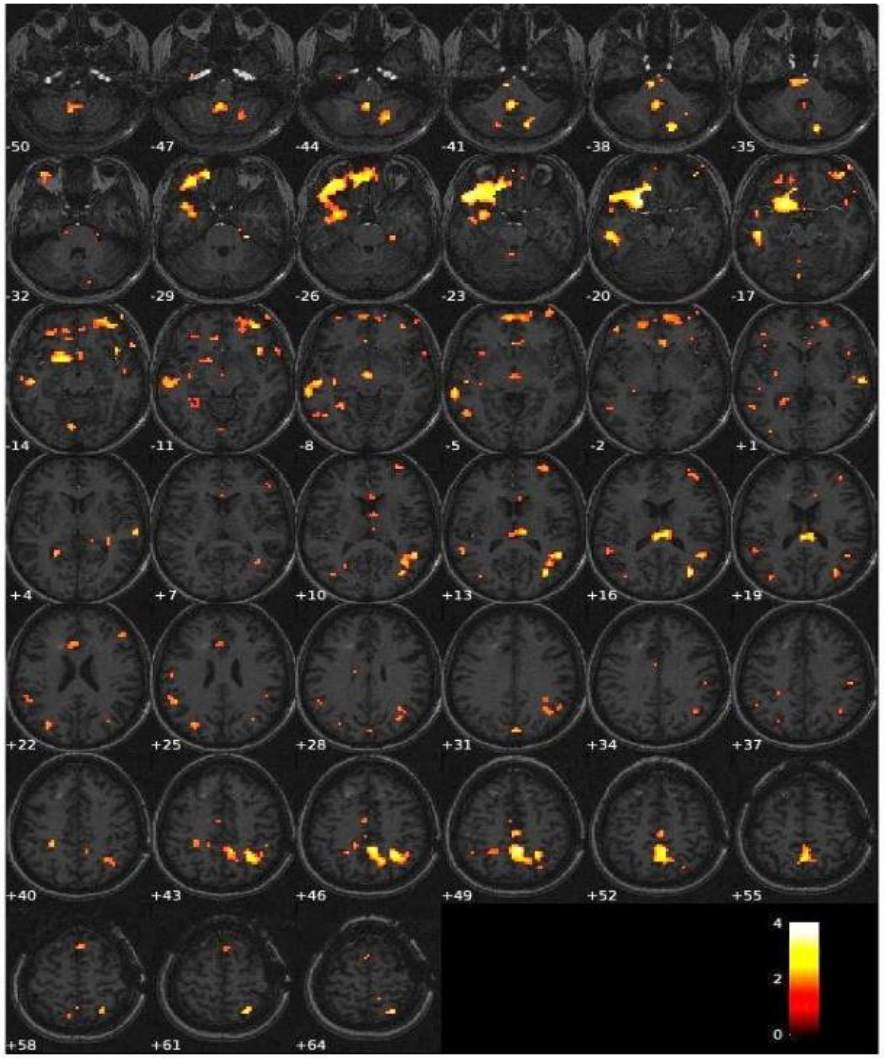


Figure 5. fMRI changes in dystonia DBS patients can significantly explain variance in individual clinical outcome. Predicted improvement - based on the magnitude of ALFF change in PM, PoG, and SPL (A) with DBS $ON_{optimal}$>DBS OFF - was correlated with actual improvement in all 11 participants (B). The magnitude of change in these areas when DBS was turned ON (optimal settings) could significantly explain over 40% of the variance in clinical outcome (R^2=0.41; p=0.03). A = anterior; ALFF = amplitude of low frequency fluctuations; D = dorsal; L = left; p = posterior; PM = premotor; PoG = postcentral gyrus; R = right; SPL = superior parietal lobule; V = ventral

fMRI in DBS dystonia

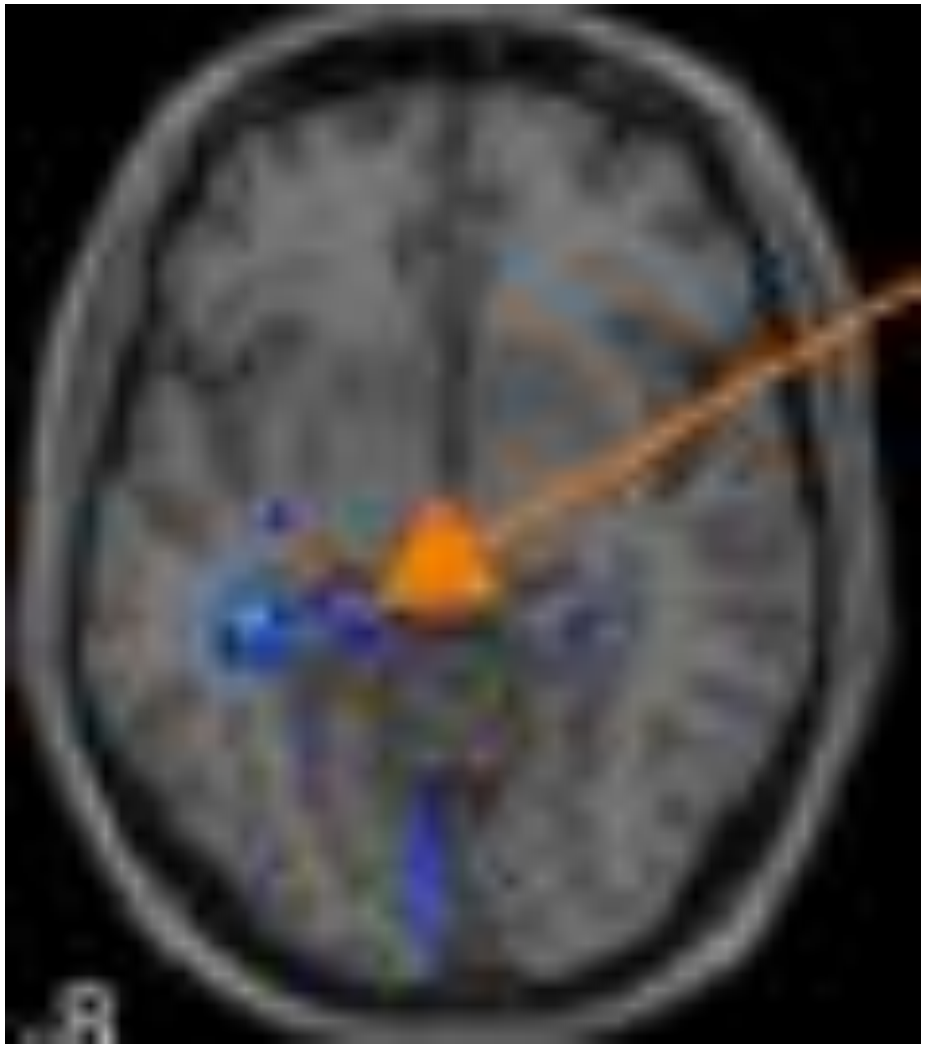
- La estimulación en contacto óptimo produce una “firma” específica en la resonancia magnética funcional
- Si esto ocurre en pacientes de novo, el punto final de la programación podría convertirse en seleccionar los parámetros de estimulación que dan lugar a este cambio en la actividad del circuito cerebral.
- No tiene que esperar una respuesta clínica de larga latencia para guiar la programación de DBS.
- Podría ser la base para una programación basada en biomarcadores sobre el ensayo clínico y el error durante semanas o meses.

Area 25
Depression



Orbitl frontal
Medial frontal
Cingulate

Fornix
Alzheimer’s



Hippocampus

¿Qué sigue?

- Ensayo clínico de programación de parámetros de estimulación de DBS con fMRI vs neurólogo en pacientes con EP con STN DBS.
- Determinar si la resonancia magnética funcional podría usarse para programar de novo a pacientes con distonía recién operada.
- ¿Se puede usar fMRI para programar depresión, TOC, epilepsia, Alzheimer y otros?

MRI-based DBS programming
Conclusions

- La estimulacion de contactos óptimos activan el circuito motor.
- El patrón de respuestas cerebrales de contactos óptimos y voltajes óptimos es distincto de los contactos no óptimales.
- Esto sugiere que la programación de DBS basada en resonancia magnética podría ser útil.
- Quizas es más importante, en trastornos donde hay un largo retraso entre la estimulación y el beneficio clínico.
- Un paso hacia el sistema de programación autonoma
- .

Colleagues

- Neurology/Psychiatry

  David Tang Way, Richard Wennberg, Anthony Lang

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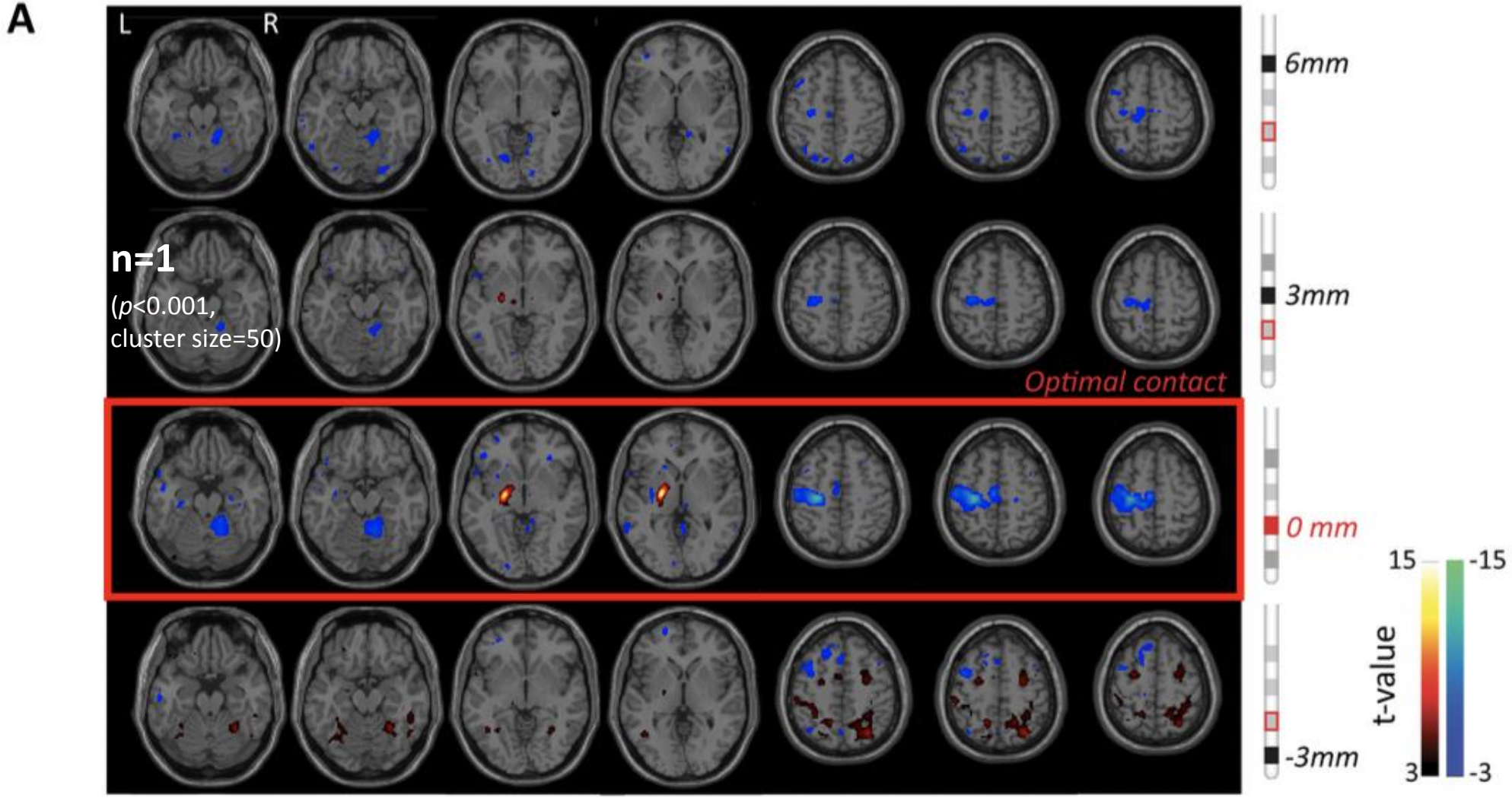
  Suneil Kalia, Elise Gondard, Irene Harmsen, Gavin Elias, Anton Fomento

- Corporate: GE, Insightec, Boston Scientific, Functional Neuroneuromodulation

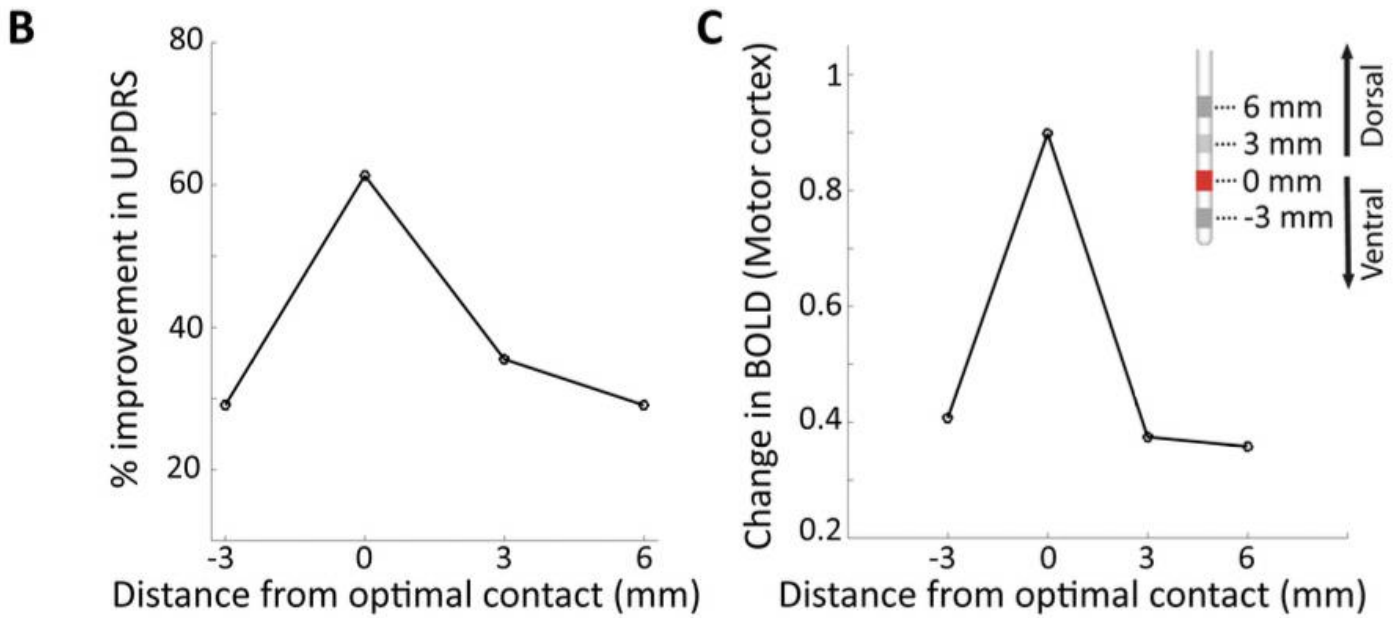
Fellows- 70 talented fellows, PhD students from throughout the world.

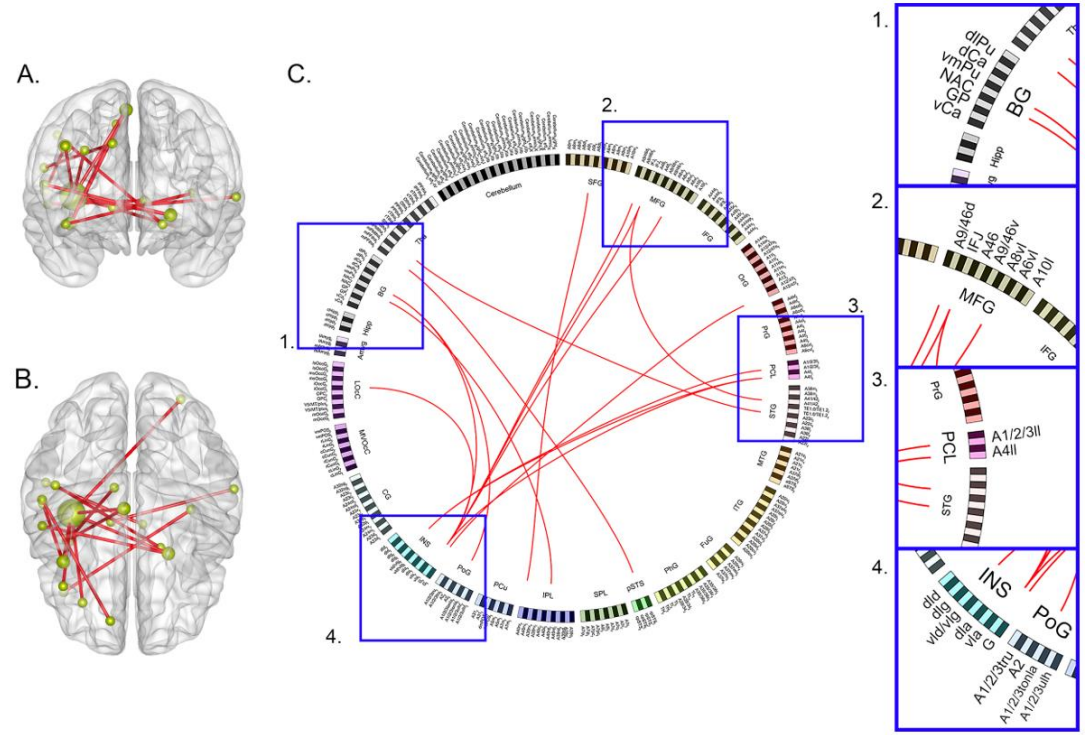
fMRI patterns generated with STN DBS N=1

LEFT DBS ON



fMRI patterns generated with STN DBS N=1





Basal Ganglia

Medial Frontal Cortex

Paracentral Lobule

Post Central Gyrus
Insula

Figure 4. DBS on optimal settings is associated with increased functional connectivity between distributed regions. Increased functional connectivity between given regions are denoted by red lines. These connections (i.e. edges) are shown in 3D anatomical space (A and B) and graphically (C). Nodes are shown as yellow spheres (A and B) or coloured rectangles (C). Labels on the inner aspect of the circle graph (C) denote broad anatomical regions, while labels on the outer aspect denote more specific regions. Dark coloured rectangles denote regions in the left hemisphere, while light coloured rectangles denote regions in the right hemisphere. Regions are parcellated according to the Human Brainnetome Atlas(Fan *et al.*, 2016). A1/2/3tonla = area 1/2/3(tongue and larynx region);A1/2/3tru = area 1/2/3(trunk region); A1/2/3ulh = area 1/2/3(upper limb, head and face region); A1/2/3ll = area 1/2/3 (lower limb region); A2 = area 2; A4ll = area 4(lower limb region); A6vl = ventrolateral area 6; A8vl = ventrolateral area 8; A9/46d = dorsal area 9/46; A10l = lateral area 10; A46 = area 46; Amyg = amygdala; BG = basal ganglia; CG = cingulate gyrus; dCA = dorsal caudate; dla = dorsal agranular insula; dld = dorsal dysgranular insula; dlg = dorsal granular insula; dlPu = dorsolateral putamen; FuG = Fusiform gyrus; G = hypergranular insula; GP = globus pallidus; Hippo = hippocampus; IFG = inferior frontal gyrus; IFJ = inferior frontal junction; INS = insula; IPL = Inferior parietal lobule; ITG = Inferior temporal gyrus; LOcC = lateral occipital cortex; MFG = middle frontal gyrus; MTG = Middle temporal gyrus; MVOcC = MedioVentral occipital cortex; NAC = nucleus accumbens; OrG = orbital gyrus; PCL = paracentral lobule; PCu = ; PhG = ; PoG = postcentral gyrus; PrG = precentral gyrus ; pSTS = posterior superior temporal sulcus; SFG = Superior frontal gyrus; SPL = Superior parietal lobule; Tha = thalamus; vCA = ventral caudate; vla = ventral agranular insula; vld = ventral dysgranular insula; vlg = ventral granular insula; vmPU = ; ventromedial putamen